OPTICAL NANOWIRE BIOSENSOR BASED ON ENERGY TRANSFER

The present invention relates to methods and apparatus for detecting the presence and/or amount of biochemical or biological molecules, as well as biochemical or biological or chemical analysis.

The introduction of micro-arrays or biochips is revolutionising the analysis of DNA (desoxyribonucleic acid), RNA (ribonucleic acid) and proteins. Applications are e.g. human genotyping (e.g. in hospitals or by individual doctors or nurses), bacteriological screening, biological and pharmacological research.

Biochips, also called biosensor chips, biological microchips, gene-chips or DNA chips, consist in their simplest form of a substrate on which a large number of different probe molecules are attached, on well defined regions on the chip, to which molecules or molecule fragments that are to be analysed can bind if they are perfectly matched. For example, a fragment of a DNA molecule binds to one unique complementary DNA (c-DNA) molecular fragment. The occurrence of a binding reaction can be detected, e.g. by using fluorescent markers that are coupled to the molecules to be analysed. This provides the ability to analyse small amounts of a large number of different molecules or molecular fragments in parallel, in a short time. One biochip can hold assays for 1000 or more different molecular fragments. It is expected that the usefulness of information that can become available from the use of biochips will increase rapidly during the coming decade, as a result of projects such as the Human Genome Project, and follow-up studies on the functions of genes and proteins.

Whereas in a first generation of biochips that is now commercially available from e.g. Affymetrix, the substrate has only a support function, in future generations the substrate is expected to contain electronics that fulfil some or all detection and control functions (e.g. measurement of temperature and pH). This has the following advantages:

- it makes the use of expensive and large optical detection systems unnecessary,
- it provides the possibility to further enhance the areal density of probed molecules,

- it enhances speed and accuracy,
- it decreases the amount of test volume required, and
- it decreases labour cost.

Biochips will become a mass product when they provide an inexpensive method for diagnostics, regardless of the venue (not only in hospitals but also at the other sites where individual doctors and/or nurses are present), and when their use leads to a reduction of the overall cost of disease management.

Nanowire-based nanosensors have recently been put forward for highly sensitive and selective detection of biological and chemical species. Nanowires are used as chemical gates in field effect transistor (FET) structures. Binding of a molecule to the surface of the nanowire can lead to the depletion or accumulation of carriers in the "bulk" of the nanowire and the accompanying changes in the conduction of the nanowire can be measured electronically.

In "Nanowire nanosensors for highly sensitive and selective detection of biological and chemical species" by Yi Cui, Qingqiao Wei, Hongkun Park and Charles M. Lieber, Science **293**, 1289 (2001), it is demonstrated that boron-doped silicon nanowires with a functionalized surface can be used to detect pH, the protein streptavidin on a picomolar level, and Ca^{2+}. In a first aspect described in this document a silicon nanowire (SiNW) solid state FET is transformed into a pH nanosensor by modifying the silicon oxide surfaces with 3-aminopropyltriethoxysilane (APTES) to provide a surface that can undergo protonation and deprotonation, where changes in the surface charge can chemically gate the SiNW. In a further aspect, biomolecular sensors are explored by functionalizing SiNWs with biotin. With this biosensors it is possible to study the well-characterised ligand-receptor binding of biotin-streptavidin. The nanosensors of the above document are capable of highly sensitive and selective real-time detection of proteins. Furthermore, in another example, a Ca^{2+}-sensor is created by immobilising calmodulin onto SiNW devices for sensing Ca^{2+} ions which are important for activating biological processes such as muscle contraction, protein secretion, cell death.

The nanosensors as described above have some disadvantages in using nanowires as a chemical gate material. These relate to contacting the nanowires as well as assembly and positioning of the nanowires with respect to the contact structures. Furthermore, a CHEM-FET (Chemically Sensitive Field-Effect Transistor) has some intrinsic problems regarding sensitivity/specificity. Charged biomolecules present in the analyte will

affect the charging state of the gate and thus set a limit to the sensitivity/specificity that can be achieved.

It is an object of the present invention to provide a method and device for the detection of biological, biochemical and/or chemical species that are sensitive and selective.

The above objective is accomplished by a method and device according to the present invention. In one aspect, the present invention relates to the use of optical properties of nanowires for biomolecule detection. A proposed transduction mechanism is based on energy transfer between the biomolecule and the nanowire.

The present invention provides a device for the detection of a molecule, e.g. in an analyte, and to output a signal in accordance with this detection. The device comprises at least one nanowire with a surface and having optical properties. The surface of the at least one nanowire is provided with al least one binding site able to selectively bind a molecule. The device furthermore comprises a photodetector for detecting the optical properties of the nanowire when the molecule selectively binds to the surface and for outputting the signal.

In one embodiment of the invention, the photodetector may be a phototransistor. The photodetector may, however, also be for example any suitable photodetector such as a photodiode, a photocathode or a photoconductor.

The molecule to be selectively bound may for example be a biomolecule or a biological organism. In an embodiment of the invention, the biomolecule may be a luminescent biomolecule with a first luminescence spectrum.

According to one aspect of the invention, the nanowire may have a second luminescence spectrum. The nanowire may be such that the first luminescence spectrum is different from the second luminescence spectrum. Furthermore, the at least one nanowire may comprise an activator ion.

In an embodiment of the present invention, the molecule to be selectively bound may be labelled with a dye.

Moreover, the device according to the present invention may comprise an array of nanowires. In an embodiment, at least a first nanowire may be modified with at least one first binding site and at least a second nanowire may be modified with at least one second binding site. The first and second binding sites may bind different molecules. In this way it is possible to detect more than one molecule at the same time with the same sensor device. Furthermore, the device may comprise at least two nanowires with different sizes.